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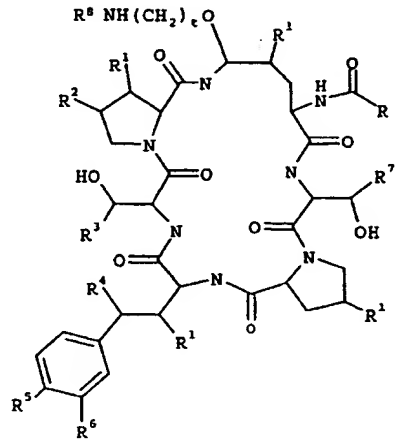

(I)

(57) Abstract: A compound represented by structure (I) is described where R^8 represents a sugar moiety. The compounds are shown to be useful as an antifungal and antiparasitic agent or as an intermediate to such an agent. Methods of treatment and pharmaceutical formulations containing compounds represented by structure (I) are also described.

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(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

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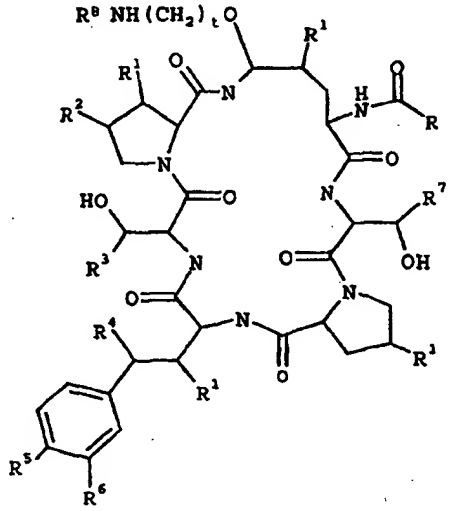

(I)

(57) Abstract

A compound represented by structure (I) is described where R^8 represents a sugar moiety. The compounds are shown to be useful as an antifungal and antiparasitic agent or as an intermediate to such an agent. Methods of treatment and pharmaceutical formulations containing compounds represented by structure (I) are also described.

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CYCLIC PEPTIDE ANTIFUNGAL AGENTS HAVING A SUGAR SUBSTITUENT

TECHNICAL FIELD

The invention relates to anti-fungal/anti-parasitic agents. in particular, derivatives of Echinocandin compounds and their use in treatment of fungal and parasitic infections.

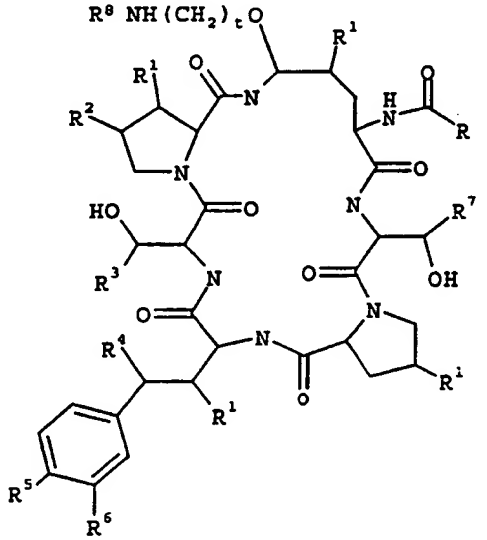
BACKGROUND ART

A number of naturally occurring cyclic peptides are known in the art including Echinocandin B (A30912A), Aculeacin, Mulundocandin, Sporiofungin, L-671,329, and S31794/F1. In general, these cyclic peptides can be structurally characterized as a cyclic hexapeptide core (or nucleus) with an acylated amino group on one of the core amino acids. This acyl group is typically a fatty acid moiety forming a side chain off the nucleus. For example, Echinocandin B has a linoleoyl side chain while Aculeacin has a palmitoyl side chain.

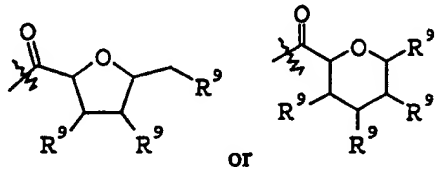
These natural products have limited inherent antifungal and antiparasitic properties. The natural compounds can be structurally modified to enhance these properties or improve the compound's stability and/or water solubility. Turner et al., *Cur. Pharm. Des.* 2:209 (1996). For example, the fatty acid side chain can be removed from the cyclic peptide core to provide an amino nucleus which can then be re-acylated to provide semi-synthetic compounds.

DISCLOSURE OF THE INVENTION

A compound represented by the following structure I is provided.

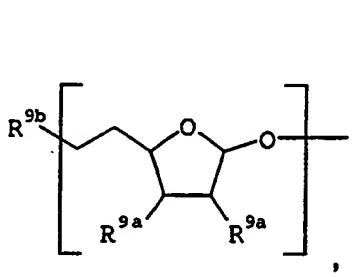


where R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R^1 is independently -H, -OH or -O-Pg; R^2 is -H, $-CH_3$, $-NH_2$, or -NH-Pg; R^3 is -H, $-CH_3$, $-CH_2CONH_2$, -CH_2CONH-Pg, $-CH_2CH_2NH_2$, or -CH_2CH_2NH-Pg; R^4 is -H, -OH, or -O-Pg; R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy; R^6 is -H, -OH, or $-OSO_3H$; R^7 is -H or $-CH_3$; t is an integer from 2-7; R^8 is a sugar moiety of the formula



or

where R^9 is independently -H, -OH, $-N_3$, -O-Pg, $-NH_2$, -NH-Pg, or a second sugar moiety comprising one to three sugar units selected from the group consisting of



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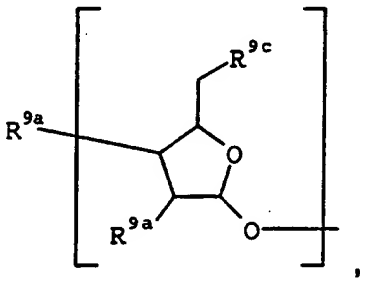

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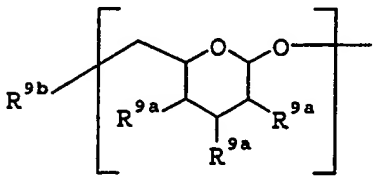

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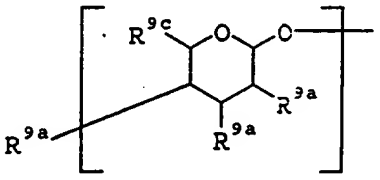


, and mixtures thereof, where R^{9a} is -H, -OH, $-N_3$, $-NH_2$, -O-Pg, or -NH-Pg, R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg, R^{9c} is $-CH_3$, $-CH_2OH$, $-CH_2N_3$, $-CH_2OSO_3H$, $-CH_2NH$-Pg, $-CH_2O$-Pg, $-CO_2H$, or $-CO_2$-Pg, where R^a is as defined above, and so long as no more than one R^9 is represented by said second sugar moiety; Pg is a protecting group (i.e., -O-Pg is a hydroxy protecting group, -NH-Pg is an amino protecting group, $-CH_2CONH$-Pg is an amido protecting group and $-CO_2$-Pg

is a carboxy protecting group); and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

The invention encompasses a pharmaceutical formulation of one or more pharmaceutical carriers, diluents or excipients and a compound represented by structure I described above.

The invention further encompasses a method of inhibiting fungal and parasitic activity by administering an effective amount of a compound represented by structure I to a recipient in need of thereof.

"Alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1} containing from 1 to 30 carbon atoms unless otherwise indicated. The alkane radical can be straight, branched, cyclic, or multi-cyclic. The alkane radical can be substituted or unsubstituted. Similarly, the alkyl portion of an alkoxy group, alkylthio group or alkanoate have the same definition as above.

"C_1-C_{12} alkyl" refers to a straight or branched saturated alkyl chain having from one to twelve carbon atoms. C_1-C_{12} alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 5-methylpentyl, hexyl, heptyl, 3,3-dimethylheptyl, octyl, 2-methyl-octyl, nonyl, decyl, undecyl and dodecyl. "C_1-C_{12} alkyl" includes "C_1-C_6 alkyl", "C_1-C_4 alkyl", and "C_3-C_{12} cycloalkyl."

"C_3-C_{12} cycloalkyl" refers to a cyclic saturated alkyl chain having from 3 to 12 carbon atoms. Moreover, "C_3-C_{12} cycloalkyl" includes "C_3-C_7 cycloalkyl", *i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

"C_1-C_{12} alkoxy" refers to a C_1-C_{12} alkyl group attached through an oxygen atom. C_1-C_{12} alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, sec-butoxy, n-pentoxy, 5-methyl-hexoxy, heptoxy, octyloxy, decyloxy and dodecyloxy. "C_1-C_{12} alkoxy" includes "C_1-C_6 alkoxy", "C_3-C_7 alkoxy", and "C_1-C_4 alkoxy".

"C_1-C_{12} alkylthio" refers to a C_1-C_{12} alkyl group attached through a sulfur atom. C_1-C_{12} alkylthio groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, 3-methyl-heptylthio, octylthio, and 5,5-dimethyl-hexylthio. "C_1-C_{12} alkylthio" includes "C_1-C_6 alkylthio" and "C_1-C_4 alkylthio."

"Alkenyl" refers to an acyclic hydrocarbon containing at least one carbon-carbon double bond. The alkene radical can be straight, branched, cyclic, or multi-cyclic. The alkene radical can be substituted or unsubstituted.

"Alkynyl" refers to an acyclic hydrocarbon containing at least one carbon-carbon triple bond. The alkyne radical can be straight, or branched. The alkyne radical can be substituted or unsubstituted.

"C_2-C_{12} alkynyl" refers to a straight or branched mono-alkynyl chain having from two to twelve carbon atoms. C_2-C_{12} alkynyl groups include, but are not limited to, ethynyl, 1-propyn-1-yl, 1-propyn-2-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-pentyn-3-yl, 4-pentyn-2-yl, 1-hexyn-3-yl, 3-hexyn-1-yl, 5-methyl-3-hexyn-1-yl, 5-octyn-1-yl, 7-octyn-1-yl, 4-decyn-1-yl and 6-decyn-1-yl.

"Aryl" refers to aromatic moieties having single (e.g., phenyl) or fused ring systems (e.g., naphthalene, anthracene, phenanthrene, etc.). The aryl groups can be substituted or unsubstituted. Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.).

"Heteroaryl" refers to aromatic moieties containing at least one heteratom within the aromatic ring system (e.g., pyrrole, pyridine, indole, thiophene, furan, benzofuran, imidazole, pyrimidine, purine, benzimidazole, quinoline, etc.). The aromatic moiety can be a single or fused ring system. The heteroaryl groups can be substituted or unsubstituted.

Within the field of organic chemistry and particularly within the field of organic biochemistry, it is widely understood that significant substitution of compounds is tolerated or even useful. In the present invention, for example, the term alkyl group allows for substituents which are a classic alkyl, such as methyl, ethyl, propyl, *n*-butyl, *i*-butyl, *t*-butyl, hexyl, isooctyl, dodecyl, stearyl, etc. The term group specifically envisions and allows for substitutions on alkyls which are common in the art, such as hydroxy, halogen, alkoxy, carbonyl, keto, ester, carbamato, etc., as well as including the unsubstituted alkyl moiety. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. The same is true for each of the other groups (i.e., aryl, alkynyl, alkenyl, heteroaryl). Suitable substituents for any of the groups defined above include alkyl, alkenyl, alkynyl, aryl, halo, hydroxy, alkoxy, aryloxy, mercapto,

alkylthio, arylthio, mono- and di-alkyl amino, quaternary ammonium salts, aminoalkoxy, hydroxyalkylamino, aminoalkylthio, carbamyl, carbonyl, carboxy, glycolyl, glycyl, hydrazino, guanyl, and combinations thereof.

"Halo" refers to chloro, fluoro, bromo and iodo.

"O-Pg" and "hydroxy protecting group" refer to a substituent of a hydroxy group that is commonly employed to block or protect the hydroxy functionality while reactions are carried out on other functional groups on the compound. This substituent, when taken with the oxygen to which it is attached, can form an ether, *e.g.*, methyl, methoxymethyl, and benzyloxymethyl ether, a silyl ether, an ester, *e.g.* acetoxy, or a sulfonate moiety, *e.g.* methane and p-toluenesulfonate. The exact genus and species of hydroxy protecting group is not critical so long as the derivatized hydroxy group is stable to the conditions of subsequent reaction(s) and the protecting group can be removed at the appropriate point without disrupting the remainder of the molecule. A preferred hydroxy protecting group is acetyl. Specific examples of hydroxy protecting groups are described in Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., (2nd ed., 1991), (*"Greene"*) chapters 2 and 3 and in the Preparations and Examples sections which follow.

"NH_p-Pg" and "amino protecting group" refer to a substituent of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. When p is 0, the amino protecting group, when taken with the nitrogen to which it is attached, forms a cyclic imide, *e.g.*, phthalimido and tetrachlorophthalimido. When p is 1, the protecting group, when taken with the nitrogen to which it is attached, can form a carbamate, *e.g.*, methyl, ethyl, and 9-fluorenylmethylcarbamate; or an amide, *e.g.*, N-formyl and N-acetylamide. The exact genus and species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and the protecting group can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino protecting group(s). Preferred amino protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl, phthalimido, and benzyloxycarbonyl (CbZ). Further examples of groups referred to by the above terms are described in *Greene* at chapter 7.

"-CO_2-Pg" and "carboxy protecting group" refer to a substituent of a carbonyl that is commonly employed to block or protect the carboxy functionality while reactions are carried out on other functional groups on the compound. This substituent, when taken with the carbonyl to which it is attached, can form an ester, *e.g.*, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, benzyl, substituted benzyl, benzhydryl, substituted benzhydryl, trityl, substituted trityl, and trialkylsilyl ester. The exact species of carboxy protecting group is not critical so long as the derivatized carboxy group is stable to the conditions of subsequent reaction(s) and the protecting group can be removed at the appropriate point without disrupting the remainder of the molecule. Other examples of groups referred to by the above terms are described in *Greene*, at chapter 5.

"C(O)NH-Pg" and "amido protecting group" refer to a substituent of an amide commonly employed to block or protect the amino portion while reacting other functional groups on the compound. This protecting group, when taken with the nitrogen to which it is attached, can form an amide, *e.g.* N-allyl, N-methoxymethyl, and N-benzyloxymethyl amide. The exact species of amido protecting group employed is not critical so long as the derivatized amido group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and the protecting group can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amido protecting group(s). Other examples of groups referred to by the above terms are described in *Greene*, at chapter 7, pg. 397.

"Carbonyl activating group" refers to a substituent of a carbonyl that promotes nucleophilic addition reactions at that carbonyl. Suitable activating substituents are those which have a net electron withdrawing effect on the carbonyl. Such groups include, but are not limited to, alkoxy, aryloxy, nitrogen containing aromatic heterocycles, or amino groups such as oxybenzotriazole, imidazolyl, nitrophenoxy, pentachlorophenoxy, N-oxysuccinimide, N,N'-dicyclohexylisoure-O-yl, N-hydroxy-N-methoxyamino; acetates, formates, sulfonates such as methanesulfonate, ethanesulfonate, benzenesulfonate, or p-tolylsulfonate; and halides such as chloride, bromide, or iodide.

"Pharmaceutical" or "pharmaceutically acceptable" means substantially non-toxic and substantially non-deleterious to the recipient. "Pharmaceutical formulation"

means that the carrier, solvent, excipients and salt are compatible with the active ingredient of the formulation (i.e., Compound I).

"Pharmaceutical salt" or "pharmaceutically acceptable salt" refers to salts of the compounds represented by structure I that are substantially non-toxic to the recipient at the doses administered. Typical pharmaceutical salts include those prepared by reaction of the compounds of the invention with a mineral or organic acid or inorganic base. Such salts are known as acid addition and base addition salts. For further exemplification, see *e.g.* Berge et al., *J. Pharm. Sci.*, 66:1 (1977).

"Solvate" is an aggregate that comprises one or more molecules of the solute, such as a formula I compound, with one or more molecules of a pharmaceutical solvent, including, but not limited to, water and ethanol. "Suitable solvent" is any solvent, or mixture thereof, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

"Thermodynamic base" is a base that provides a reversible deprotonation of an acidic substrate or is a proton trap for protons produced as reaction byproducts, and is reactive enough to effect the desired reaction without significantly effecting any undesired reactions. Examples of thermodynamic bases include, but are not limited to, acetates, acetate dihydrates, carbonates, bicarbonates, C_1-C_4 alkoxides, and hydroxides (*e.g.* silver, lithium, sodium, or potassium acetate, acetate dihydrate, carbonate, bicarbonate, methoxide, or hydroxide), tri-(C_1-C_4 alkyl)amines, or aromatic nitrogen containing heterocycles (*e.g.* imidazole and pyridine).

"Inhibiting" includes prohibiting, stopping, retarding, alleviating, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of the growth or any attending characteristics, symptoms, and results from the existence of a parasite or fungus. These methods include both medical therapeutic (acute) and/or prophylactic (prevention) administration as appropriate.

"Effective amount" refers to an amount of a compound of formula I which is capable of inhibiting fungal and/or parasitic activity.

"Recipient" includes mammals, preferably, humans.

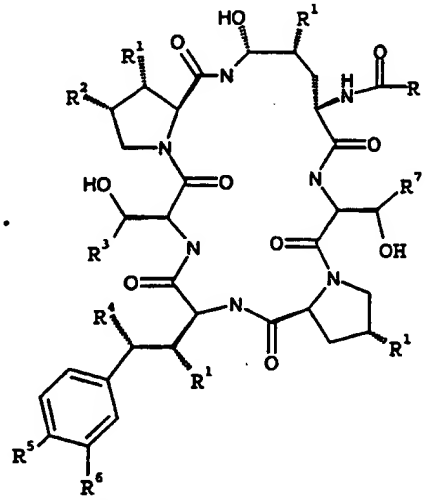
BEST MODE FOR CARRYING OUT THE INVENTION

Compounds represented by structure I have now been found to be useful as antifungal and antiparasitic agents or as an intermediate thereof. The most convenient

means of producing compounds represented by structure I is by modifying naturally occurring compounds.

For illustrative purposes, Scheme I (below) starts with a specific Echinocandin derivative. However, one could begin with any natural product, semi-synthetic or synthetic Echinocandin-type compound containing a hemiaminal group.

The term "Echinocandin-type compounds" refers to compounds having the following general structure including any simple derivatives thereof:



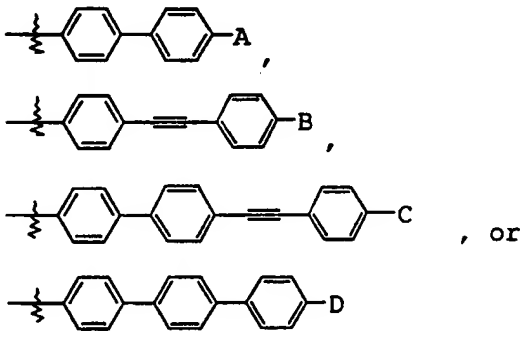
wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R^1 is -H or -OH; R^2 is -H, $-NH_2$ or $-CH_3$; R^3 is -H, $-CH_3$, $-CH_2CONH_2$ or $-CH_2CH_2NH_2$; R^4 is -H or -OH; R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy; R^6 is -H, -OH, or $-OSO_3H$; R^7 is -H or $-CH_3$; and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

"Natural product" is those secondary metabolites, usually of relatively complex structure, which are of more restricted distribution and more characteristic of a specific source in nature. Suitable natural product starting materials of the Echinocandin cyclopeptide family include Echinocandin B, Echinocandin C, Aculeacin Aγ, Mulundocandin, Sporiofungin A, Pneumocandin A_0, WF11899A, and Pneumocandin B_0.

The cyclic peptides used in the invention can be produced by culturing various microorganisms. In general, the cyclic peptides can be characterized as a cyclic hexapeptide nucleus with an acylated amino group on one of the amino acids. The

amino group on the naturally-occurring cyclic peptide is typically acylated with a fatty acid group forming a side chain off the nucleus. Examples of naturally-occurring acyl groups include, but are not limited to, linoleoyl (Echinocandin B, C and D), palmitoyl (Aculeacin A$_\gamma$ and WF11899A), stearoyl, 12-methylmyristoyl (Mulundocandin), 10,12-dimethylmyristoyl (Sporiofungin A and Pneumocandin A$_0$).

Semi-synthetic derivatives can be generally prepared by removing the fatty acid side chain from the cyclic peptide nucleus to produce a free amino group (i.e., no pendant acyl group -C(O)R). The free amine is then re-acylated with a suitable acyl group. For example, the echinocandin B nucleus has been re-acylated with certain nonnaturally occurring side chain moieties to provide a number of antifungal agents. U.S. Patent No. 4,293,489. The N-acyl side chain encompasses a variety of side chain moieties known in the art. Suitable side chain moieties include substituted and unsubstituted alkyl groups, alkenyl groups, alkynyl groups, aryl groups, heteroaryl groups and combinations thereof. Preferably, the side chain contains both a linearly rigid section and a flexible alkyl section to maximize antifungal potency. Representative examples of preferred acyl side chains include R groups having the following structures:

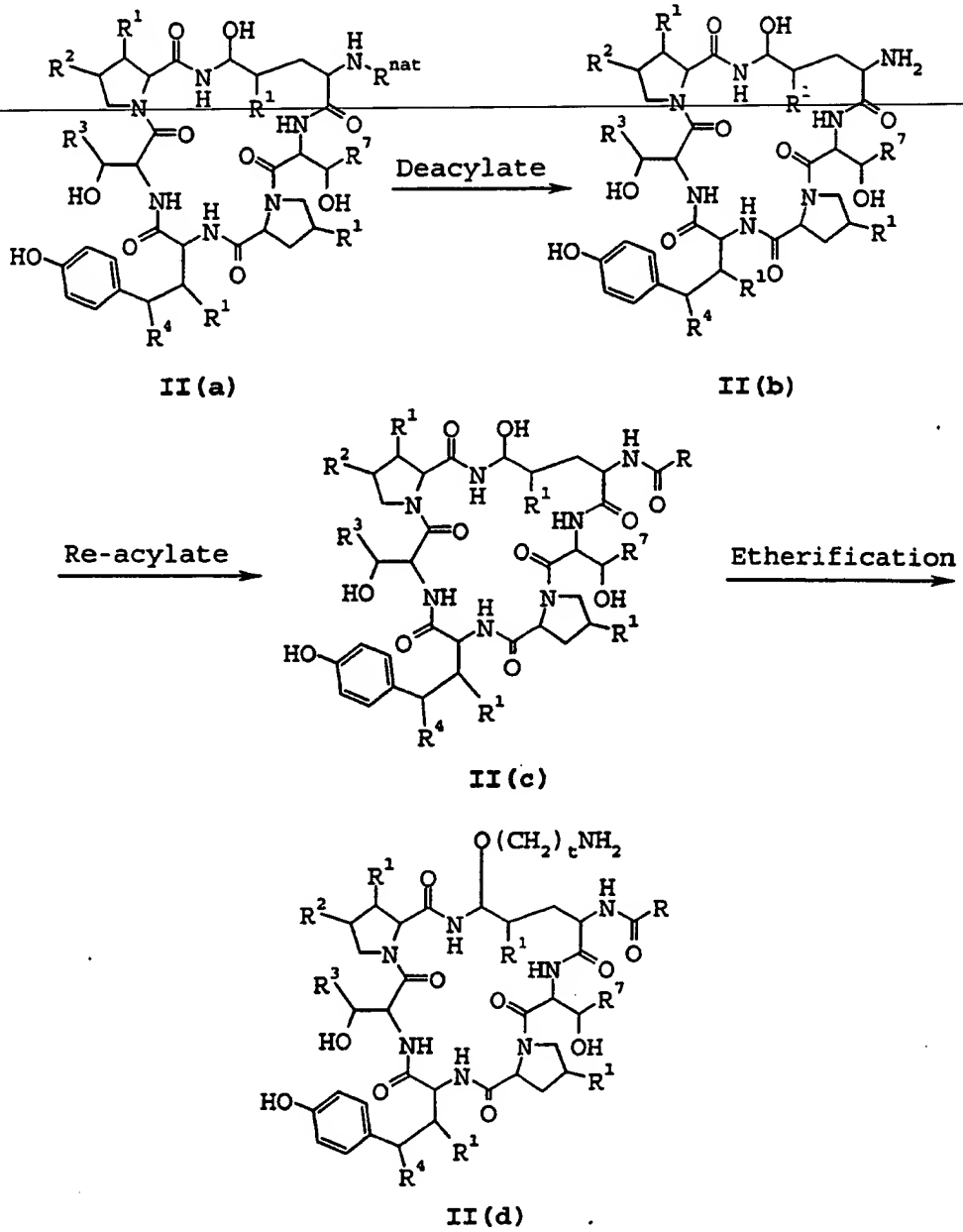


, or

where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or -O-$(CH_2)_m$-[O-$(CH_2)_n$]$_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E; m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4; X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

Scheme I illustrates the general semi-synthetic route described above where a natural product (Compound II(a)) is modified to provide an intermediate (Compound

II(d)) which is then further modified to provide a representative example of Compound I as illustrated in Scheme II.



Scheme I

Cyclic peptides represented by structure II(a) can be prepared by fermentation of known microorganisms. For example, the cyclic peptide II(a) where R^1 and R^4 are each hydroxy, R^2, R^3 and R^7 are each methyl (cyclic nucleus corresponding to A-

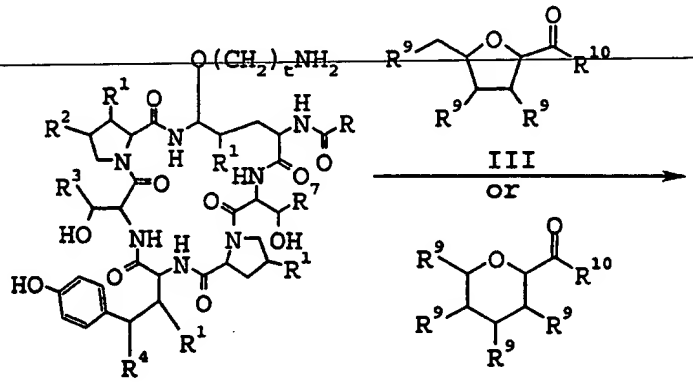
30912A) can be prepared using the procedure detailed in U.S. Patent No. 4,293,482. Cyclic peptide II(a) where R^1 is hydroxy, R^2, R^3 and R^7 are each methyl, and R^4 is hydrogen (cyclic nucleus corresponding to A-30912B) can be prepared using the procedure detailed in U.S. Patent No. 4,299,763. Aculeacin can be prepared using the procedure detailed in U.S. Patent No. 3,978,210. Cyclic peptide II(a) where R^3 is $CH_2C(O)NH_2$, R^7 is methyl, R^2 is hydrogen, and R^1 and R^4 are hydroxy can be prepared using the procedure detailed in U.S. Patent No. 5,198,421.

Cyclic peptide II(a) can be deacylated using procedures known in the art to provide an amino nucleus represented by structure II(b). This reaction is typically carried out enzymatically by exposing the naturally occurring cyclic peptide to a deacylase enzyme. The deacylase enzyme can be obtained from the microorganism *Actinoplanes utahensis* and used substantially as described in U.S. Patent Nos. 4,293,482 and 4,304,716. The deacylase enzyme can also be obtained from the *Pseudomonas* species. Deacylation can be accomplished using whole cells of *A. utahensis* or *Pseudomonas* or the crude or purified enzyme thereof or using an immobilized form of the enzyme. See European Patent Application No. 0 460 882. Examples of naturally occurring cyclic peptides that can be used as starting materials include, but are not limited to, aculeacin (palmitoyl side chain), tetrahydroechinocandin B (stearoyl side chain), mulundocandin (branched C_{15} side chain), L-671,329 (C_{16} branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C_{15} branched side chain), FR901379 (palmitoyl side chain). A preferred cyclic peptide is echinocandin B (Compound II(a) where R^1 and R^4 are each hydroxy, R^2, R^3 and R^7 are each methyl, and R^{nat} is linoleoyl).

The amino nucleus II(b) can be re-acylated, by procedures taught in U.S. Patent Nos. 5,646,111, and 5,693,611 to provide compounds represented by structure II(c). See Preparation 12 below for an example of this transformation. Also see, U.S. Patent Nos. 5,646,111 and 5,693,611 for preparation of the acyl groups at R. Cyclic peptides II(c) where R contains 1 or more heterocyclic rings can be prepared as taught in U.S. Patent No. 5,693,611.

Compound II(d) can then be prepared by selective etherification of Compound II(c) as taught in *J. Antibiotics*, 51:239-242 (1998) and U.S. Patent No. 5,652,213.

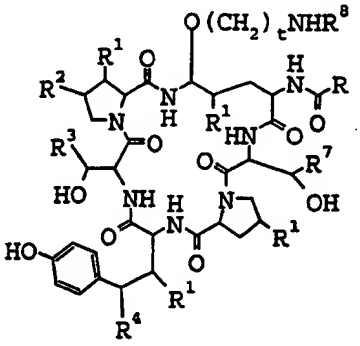
The compounds represented by structure I can be prepared from compounds of structure II(d) as illustrated in Scheme II below where R^{10} is a carbonyl activating group and t, R, R^1, R^2, R^3, R^4, R^7 and R^9 are as defined above.



II(d)

III
or

IV



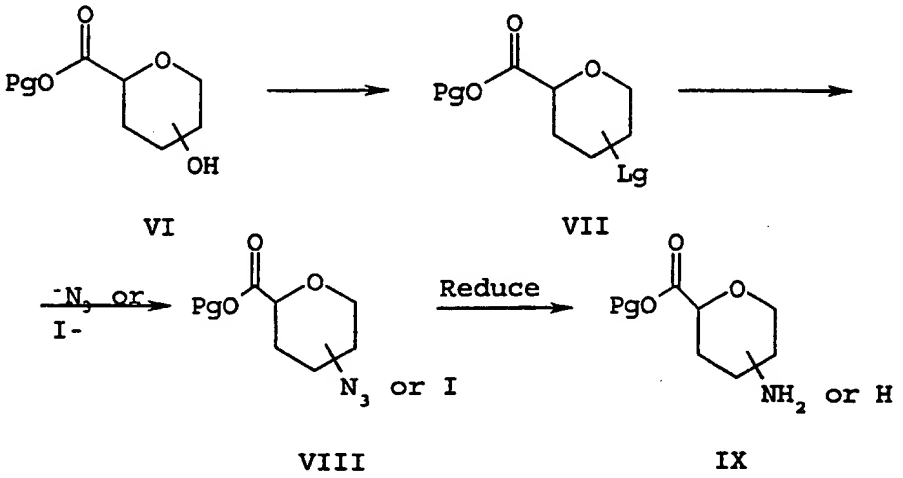
I

Scheme II

Compound I can be prepared by adding either Compound III or IV to Compound II(a) dissolved or suspended in a suitable solvent in the presence of a suitable thermodynamic base. A convenient and preferred solvent for the reaction is dimethylformamide while a convenient and preferred base is triethylamine. The reaction can be performed at from 0°C to the reflux temperature of the mixture but is typically performed at ambient temperatures for about 24 hours. See Example 1 below for an example of specific reaction conditions.

Compounds represented by structures III and IV are known in the art and if not commercially available can be synthesized by techniques well known in synthetic chemical arts. Collins et al., "Monosaccharides: Their Chemistry and Their Roles in Natural Products," John Wiley and Sons, New York, NY, 1995; and "Methods in Carbohydrate Chemistry", Vol VI, Academic Press, New York, N.Y., 1980.

Compounds III and IV where R^9 is hydroxy are known as carbohydrates or monosaccharides (sugars). These sugars can be modified by replacing one or more hydroxy groups with hydrogen, azide, or amino to provide the other derivatives of Compounds III and IV including disaccharides and polysaccharides where R^9 is a second sugar moiety. Such compounds can be prepared as illustrated in Scheme 3 below where Lg is an activated hydroxy leaving group.

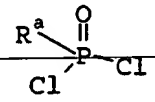


Scheme 3

A commercially available Compound VI can have its hydroxy group(s) activated for nucleophilic displacement by standard techniques known in the art. For example, the hydroxy group can be sulfonylated with methane-, benzene-, or p-toluene-sulfonyl chloride (or bromide) to provide a Compound VII where Lg is OSO_2Me, OSO_2-phenyl, or OSO_2-p-toluenyl. At this point, the leaving group can be displaced by azide ion, *e.g.*, from sodium or potassium azide. Alternatively, the leaving group can be displaced by iodide ion from, *e.g.*, sodium or potassium iodide. The resulting Compound VIII can be reduced to form a Compound IX where one or more of R^{9a} or R^{9b} is amino or hydrogen by catalytic hydrogenation or with a reducing agent such as nickel chloride hexahydrate. It is preferred that when an amino group is desired in the final product Compound I, that any azido groups are converted to amino groups after coupling to Compound II(d).

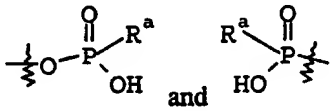
Compound I, where any of R^9 is amino can be formed from a Compound I where R^9 is azido as described by analogous procedures well known in the art. See, *e.g.*, Larock, "Comprehensive Organic Transformations," pg. 409, VCH Publishers, New York, N.Y., 1989.

Compound I where R^5, R^9, R^{9a}, R^{9b}, and/or R^{9c} is a hydroxy group, can be phosphorylated or phosphonylated by reaction with an appropriately substituted dichloro- phosphate or phosphonic acid of formula V



V

in the presence of a suitable base to provide, following an aqueous work-up, to produce Compound I where R^5, R^9, R^{9a}, R^{9b}, and/or R^{9c} are moieties of the formula



, respectively.

Suitable bases include lithium trimethylsilanolate (LiOTMS), and lithium bis(trimethylsilyl)amide (LHMDS). A preferred solvent is an aprotic solvent such as tetrahydrofuran and/or dimethylformamide. U.S. Patent No. 5,693,611.

Alternatively, the compounds represented by structure I where R^{9b} is hydroxy and/or R^{9c} is hydroxymethyl can be sulfated by reaction with a suitable sulfation reagent. Guiseley et al., *J. Org. Chem.*, 26:1248 (1961). The protected compound of structure I can have its protecting group(s) removed to form a deprotected Compound I. Initial choices of protecting groups, and methods for their removal, are well known in the art. See, *e.g.*, *Greene*.

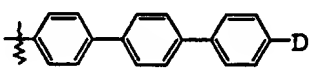
Pharmaceutical salts are typically formed by reacting Compound I with an equimolar or excess amount of acid or base. The reactants are generally combined in a mutual solvent such as diethylether, tetrahydrofuran, methanol, ethanol, isopropanol, benzene, and the like for acid addition salts, or water, an alcohol or a chlorinated solvent such as methylene chloride for base addition salts. The salts normally precipitate out of solution within about one hour to about ten days and can be isolated by filtration or other conventional methods.

Acids commonly employed to form acid addition salts are inorganic acids including, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, ethanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, tartaric acid, benzoic acid, acetic acid.

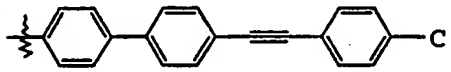
Base addition salts include those derived from inorganic bases, including, but not limited to, ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates. Bases useful in preparing salts of this invention include, but are not limited to, sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide and calcium carbonate.

The particular counterion forming a part of any salt of this invention is not of a critical nature, provided the salt as a whole is pharmacologically acceptable and the counterion does not contribute undesired qualities to the salt as a whole. Preferred pharmaceutical acid addition salts are those formed with mineral acids such as hydrochloric acid and sulfuric acid, and those formed with organic acids such as maleic acid, tartaric acid, and methanesulfonic acid. Preferred pharmaceutical base addition salts are the potassium and sodium salt forms.

Preferred compounds of the present invention are those compounds represented by structure I where R^1 is hydroxy at each occurrence; R^4 is hydroxy; R^2, R^3, and R^7 are each methyl; R is a moiety of the formula

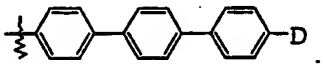


or



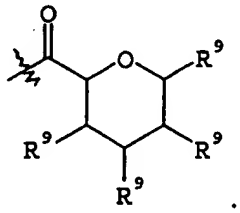
; and

R^8 is methyl or methoxy; or a pharmaceutically acceptable salt or solvate thereof. More preferable are those compounds wherein R^5 is hydroxy; R is a moiety of the formula



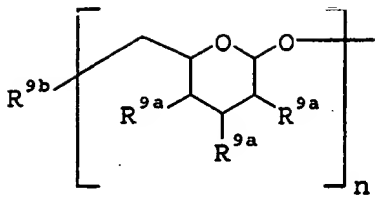
;

R^8 is a moiety of the formula:



;

D is hydrogen or C3-C7 alkoxy; R^9 is independently hydrogen, hydroxy, amino, or a moiety of the formula:



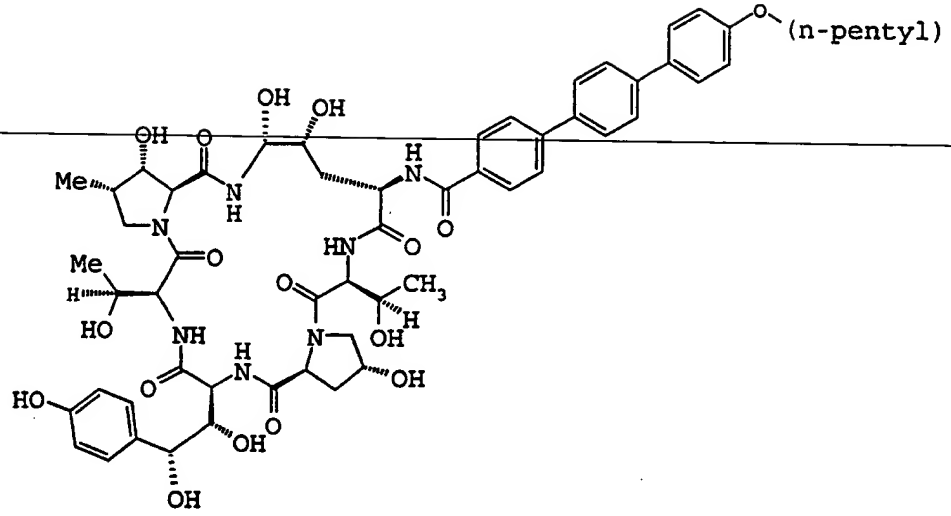
where R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg and n is 1, 2, or 3; or a pharmaceutically acceptable salt or solvate thereof. Even more preferable are those compounds wherein D is n-pentoxy; R^9 is independently hydroxy or amino; or a pharmaceutically acceptable salt or solvate thereof. Most preferred are those compounds wherein R^9 is hydroxy at each occurrence; and t is 2; or a pharmaceutically acceptable salt or solvate thereof.

The optimal time for performing the reactions of Schemes 1 - 3 can be determined by monitoring the progress of the reaction by conventional chromatographic techniques. Choice of reaction solvent is generally not critical so long as the solvent employed is inert to the ongoing reaction and sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction. Unless otherwise indicated, all of the reactions described herein are preferably conducted under an inert atmosphere. A preferred inert atmosphere is nitrogen. Once a reaction is complete, the intermediate compound can be isolated by procedures well-known in the art, for example, the compound can be crystallized or precipitated and then collected by filtration, or the reaction solvent can be removed by extraction, evaporation or decantation. The intermediate compound can be further purified, if desired, by common techniques such as crystallization, precipitation, or chromatography over solid supports such as silica gel, alumina and the like, before carrying out the next step of the reaction scheme.

The following examples are meant to illustrate but not limit the invention. All references cited herein are hereby incorporated herein by reference.

The following Preparations and Examples further describe synthesis of the compounds. "Fast atom bombardment mass spectroscopy" and "high performance liquid chromatography" are abbreviated "MS(FAB)" and "HPLC", respectively.

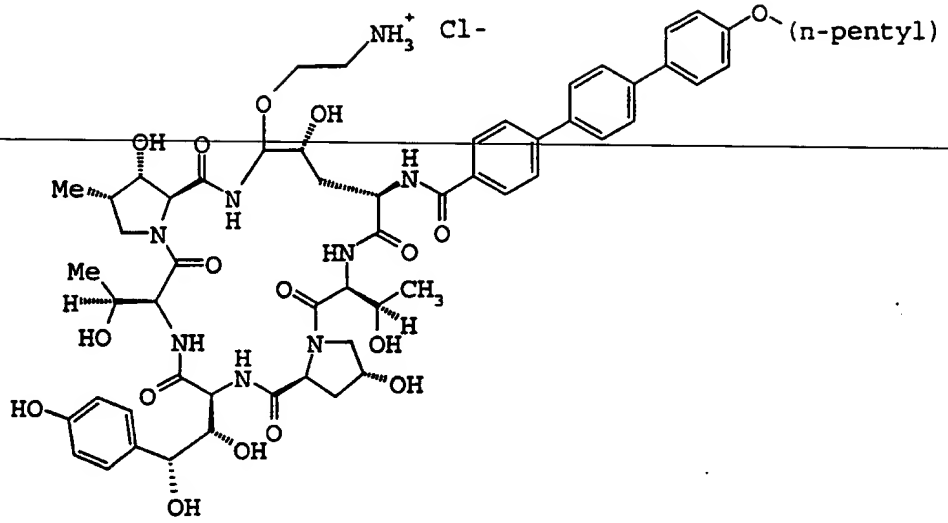
Preparation 1



The A-30912A nucleus (60.2 mmol) and the 2,4,5-trichlorophenol ester of [(4"-pentyloxy)-1,1':4',1"-terphenyl]-4-carboxylic acid (26.0 g, 48.2 mmol) were combined in 8.5 L of dimethylformamide. The resultant reaction mixture was stirred for approximately 48 hours at room temperature (RT) and the solvent was removed *in vacuo* to provide a residue. This residue was slurried in ether, collected by filtration, washed with methylene chloride and dissolved in methanol or a 1:1 (v/v) acetonitrile/water mixture. The resultant solution is subjected to reverse phase HPLC (C18; eluent of 20-40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v); 20 mL/min.; 230 nm). After removing the unreacted A30912A nucleus, the desired product is eluted from the column using an eluent of aqueous acetonitrile. The fractions containing the desired product are combined and then concentrated *in vacuo* or lyophilized to provide 18 g of the title compound.

MS(FAB): 1140.5103 (M^{+1}).

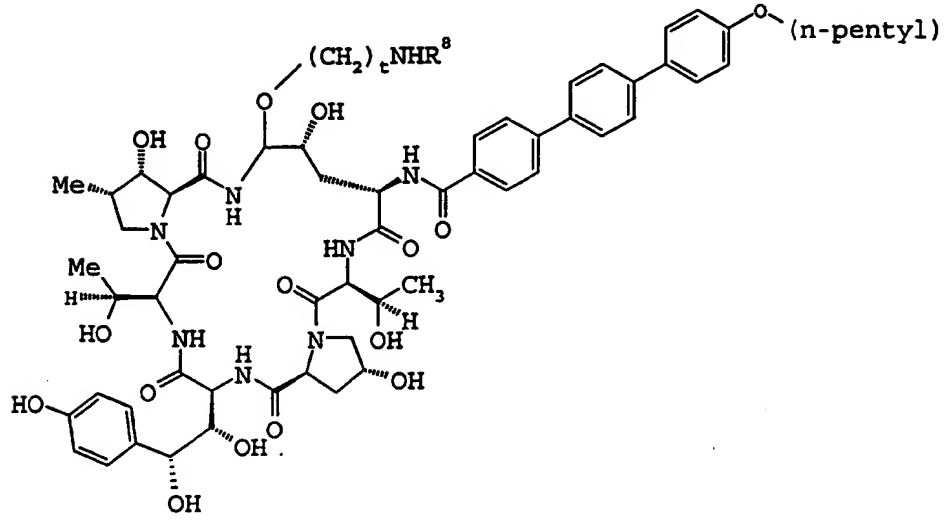
Preparation 2



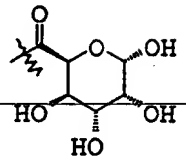
The compound of Preparation 1 (1.08 g, 0.9 mmol) and ethanolamine hydrochloride (185 mg, 1.9 mmol) were dissolved in about 20 mL of dimethylsulfoxide. Hydrogen chloride was blown over the solution for about 5 seconds. The resulting mixture was stirred at room temperature under nitrogen for 28 hours. The reaction solution was subjected to reverse-phase HPLC (C18; eluent of 60% acetonitrile in water containing 0.1% trifluoroacetic acid (v/v); 40 mL/min.; 280 nm). The fractions containing the desired product were combined and concentrated *in vacuo* or lyophilized to provide the title compound. MS(FAB):1183.5577 (M+H).

Examples 1 and 2

Examples 1 and 2 have the following base structure:



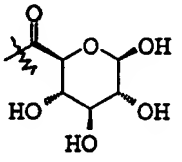
Example 1



t = 2, R^8 =

α-D-Galacturonic acid (388 mg, 2.0 mmol) and N-hydroxysuccinimide (NHS) (230 mg, 2.0 mmol) were dissolved in anhydrous dimethylformamide. The mixture was cooled in an ice bath under nitrogen and dicyclohexylcarbodiimide (DCC) (412 mg, 2.0 mmol) was added. The ice bath was removed and the resulting mixture was stirred overnight and then the reaction solution was filtered directly into a flask containing the compound of Preparation 2 (240 mg, 0.2 mmol). Triethylamine (0.030 mL, 0.2 mmol) was then added and the resulting mixture was stirred at room temperature under nitrogen for 48 hours. The resultant solution was subjected to reverse-phase HPLC (C18; eluent of 60% acetonitrile in water; 280 nm). The fractions containing the desired product were combined and then concentrated *in vacuo* or lyophilized to provide the title compound. MS(FAB): 1381 (M^-+Na).

Example 2



t = 2, R^8 =

D-Glucuronic acid (194 mg, 1.0 mmol) and the compound of Preparation 2 were converted to the title compound by the procedure of Example 1

The compounds represented by structure I have been shown to exhibit a variety of antifungal and antiparasitic activities to various degrees. For example, the compounds of structure I can inhibit the growth of various infectious fungi including *Candida spp.* (e.g., *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, *C. tropicalis*, or *C. lusitaniae*), *Torulopus spp.* (e.g., *T. glabrata*), *Aspergillus spp.* (e.g., *A. fumigatus*), *Histoplasma spp.* (e.g., *H. capsulatum*), *Cryptococcus spp.* (e.g., *C. neoformans*), *Blastomyces spp.* (e.g., *B. dermatitidis*), *Fusarium spp.*, *Trichophyton spp.*, *Pseudallescheria boydii*, *Coccidioides immitis*, *Sporothrix schenckii* and the like.

Antifungal activity of a test compound is determined *in vitro* by obtaining the minimum inhibitory concentration (MIC) of the compound using a standard agar dilution test or a disc-diffusion test. The compound is then tested *in vivo* (in mice) to determine the effective dose for controlling a systemic fungal infection.

Accordingly, representative compounds of the present invention were tested for, and displayed, antifungal activity against at least one of the following fungii: *C. albicans*, *C. parapsilosis*, *C. neoformans*, *Histoplasma spp*, and *A. fumigatus*.

The compounds also inhibit growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example, the compounds inhibit the growth of *Pneumocystis carinii* the causative organism of pneumocystis pneumonia (PCP) in AIDS and other immunocompromised recipients. "Topley and Wilson's Microbiology and Microbial Infections," Vol. 5, Ch. 22, Oxford University Press, Inc., New York, N.Y., 1998. Other protozoans that are inhibited by compounds of formula I include *Plasmodium spp.*, *Leishmania spp.*, *Trypanosoma spp.*, *Cryptosporidium spp.*, *Isospora spp.*, *Cyclospora spp.*, *Trichomonas spp.*, *Microsporidiosis spp.* and the like.

The dose of the compound represented by structure I administered varies depending on such factors as the nature and severity of the infection, the age and general health of the recipient and the tolerance of the recipient to the active ingredient. The particular dose regimen likewise can vary according to such factors and can be given in a single daily dose or in multiple doses during the day. The regimen can last from about 2 - 3 days to about 2 - 3 weeks or longer. A typical daily dose (administered in single or divided doses) contains a dosage level of from about 0.01 mg/kg to about 100 mg/kg of body weight of the active compound. Preferred daily doses are generally from about 0.1 mg/kg to about 60 mg/kg, more preferably from about 2.5 mg/kg to about 40 mg/kg.

Compound I can be administered parenterally, for example using intramuscular, sub-cutaneous, or intra-peritoneal injection, nasal, or oral means. In addition to these methods of administration, compound I can be applied topically for skin infections.

The invention also provides pharmaceutical formulations useful for administering the compounds of the invention. The active ingredient in such formulations comprises from 0.1% to 99.9% by weight of the formulation, more generally from about 10% to about 30% by weight.

For parenteral administration, the formulation comprises Compound I and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation can contain a solubilizing agent such as a polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations can be made up in sterile vials containing the active ingredient and one or more excipients in a dry powder or lyophilized powder form. Prior to use, a physiologically acceptable diluent is added and the solution withdrawn via syringe for administration to the recipient.

The pharmaceutical formulations are prepared by known procedures using known and readily available ingredients. In making the compositions of the present invention, the active ingredient will generally be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it can be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets. pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active ingredient, soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders and the like.

For oral administration, the active ingredient is filled into gelatin capsules or formed into tablets. Tablets can also contain a binding agent, a dispersant or other excipients suitable for preparing a proper size tablet for the dosage and particular compound of the formula I. For pediatric or geriatric use the active ingredient can be formulated into a flavored liquid suspension, solution or emulsion. A preferred oral formulation is linoleic acid, cremophor RH-60 and water and preferably in the amount (by volume) of 8% linoleic acid, 5% cremophor RH-60, 87% sterile water and a compound of formula I in an amount of from about 2.5 to about 40 mg/mL.

For topical use the active ingredient can be formulated with a dry powder for application to the skin formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, *e.g.*, an alcohol or glycol.

Formulations

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. The term "active ingredient" refers to a compound represented by structure I or a pharmaceutically acceptable salt thereof.

Formulation Example 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation Example 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets of 665 mg each.

Formulation Example 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation Example 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation Example 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum

heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of active ingredient per 5 mL dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

An intravenous formulation can be prepared as follows:

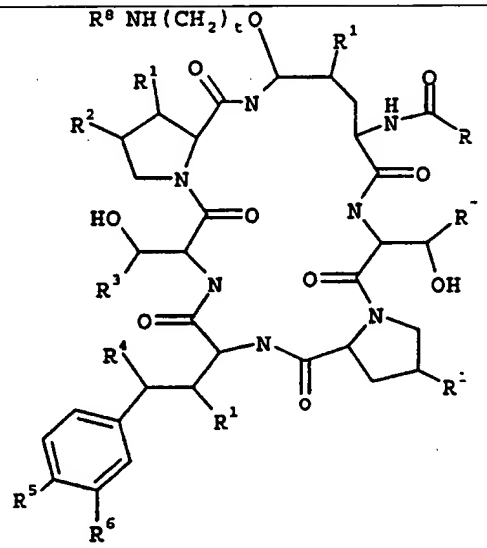
Active ingredient	100 mg
Isotonic saline	1,000 mL

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 mL per minute.

CLAIMS

WE CLAIM:

1. A compound represented by structure I:



wherein

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group;

R^1 is independently -H, -OH or -O-Pg;

R^2 is -H, $-CH_3$, $-NH_2$, or -NH-Pg;

R^3 is -H, $-CH_3$, $-CH_2CONH_2$, $-CH_2CONH$-Pg, $-CH_2CH_2NH_2$, or $-CH_2CH_2NH$-Pg;

R^4 is -H, -OH, or -O-Pg;

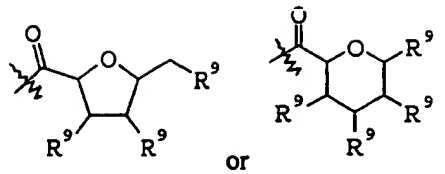
R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy;

R^6 is -H, -OH, or $-OSO_3H$;

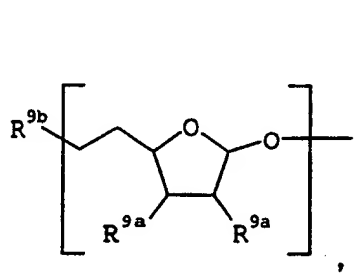
R^7 is -H or $-CH_3$;

t is an integer from 2-7;

R^8 is a sugar moiety of the formula


or

where R^9 is independently -H, -OH, $-N_3$, -O-Pg, $-NH_2$, -NH-Pg, or a second sugar moiety comprising one to three sugar units selected from the group consisting of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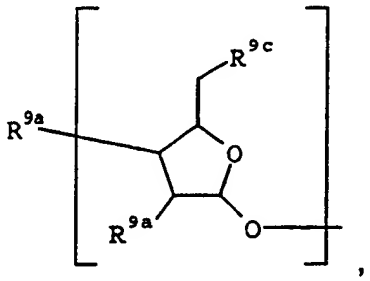
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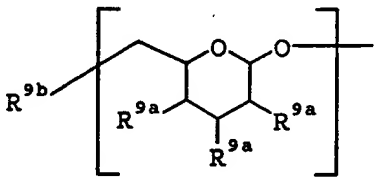
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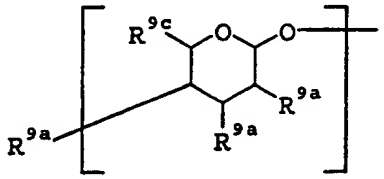

, and mixtures thereof, wherein

R^{9a} is -H, -OH, $-N_3$, $-NH_2$, -O-Pg, or -NH-Pg,

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg,

R^{9c} is $-CH_3$, $-CH_2OH$, $-CH_2N_3$, $-CH_2OSO_3H$, $-CH_2NH$-Pg, $-CH_2O$-Pg, $-CO_2H$, or $-CO_2$-Pg,

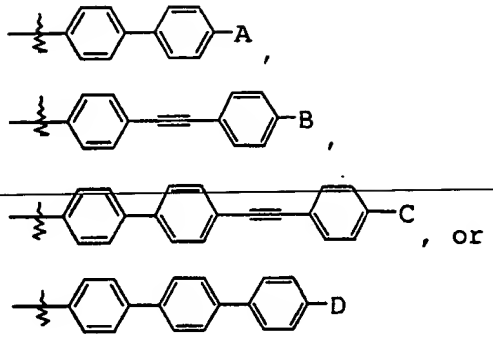
where R^a is as defined above,

and so long as no more than one R^9 is represented by said second sugar moiety;

Pg is a protecting group; and

pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

2. The compound of Claim 1 wherein R is



where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or -O-$(CH_2)_m$-[O-$(CH_2)_n$]$_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E;

m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;

X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

3. The compound of Claim 2 wherein

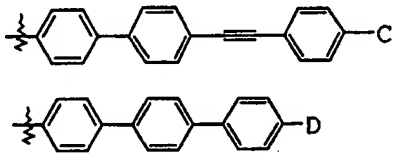
R^1 is hydroxy at each occurrence;

R^4 is hydroxy;

R^5 is -OPO_2HR^a, where R^a is methyl or methoxy;

R^2, R^3, and R^7 are each methyl; and

R is a moiety of the formula



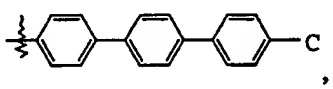
; or

a pharmaceutically acceptable salt or solvate thereof.

4. The compound of Claim 3 wherein

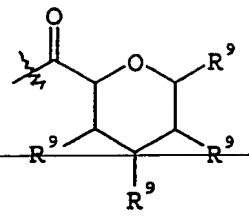
R^5 is hydroxy;

R is a moiety of the formula

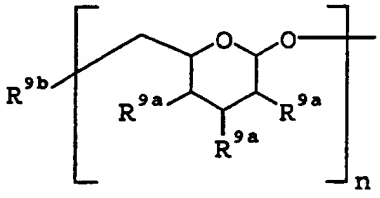


where C is hydrogen or C_3-C_7 alkoxy;

R^9 is a moiety of the formula



where R^9 is independently hydrogen, hydroxy, amino. or a moiety of the formula



; and

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg and n is 1, 2, or 3; or

a pharmaceutically acceptable salt or solvate thereof.

5. The compound of Claim 4 wherein

C is n-pentoxy;

R^9 is independently hydroxy or amino; or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 5 wherein

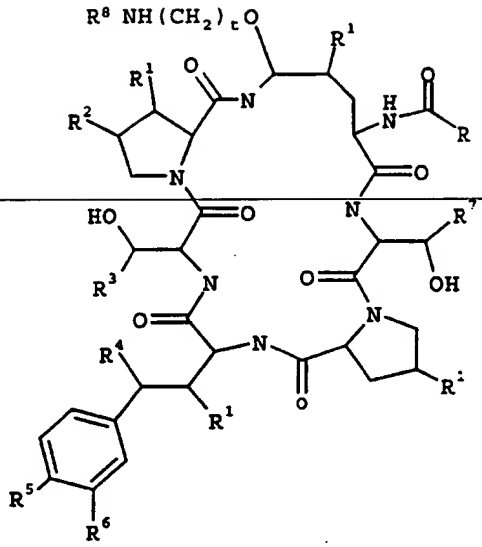
R^9 is hydroxy at each occurrence; and

t is 2; or a pharmaceutically acceptable salt of solvate thereof.

7. A pharmaceutical formulation comprising one or more pharmaceutical carriers, diluents, or excipients and

a compound of Claim 1.

8. A method of inhibiting fungal activity comprising administering to a recipient in need of such inhibition an effective amount of a compound represented by structure I:



wherein

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group;

R^1 is independently -H, -OH or -O-Pg;

R^2 is -H, $-CH_3$, $-NH_2$, or -NH-Pg;

R^3 is -H, $-CH_3$, $-CH_2CONH_2$, -CH_2CONH-Pg, $-CH_2CH_2NH_2$, or $-CH_2CH_2NH$-Pg;

R^4 is -H, -OH, or -O-Pg;

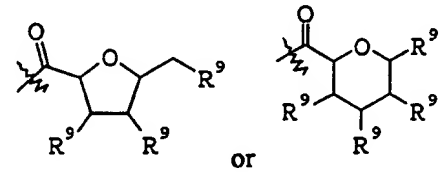
R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy;

R^6 is -H, -OH, or $-OSO_3H$;

R^7 is -H or $-CH_3$;

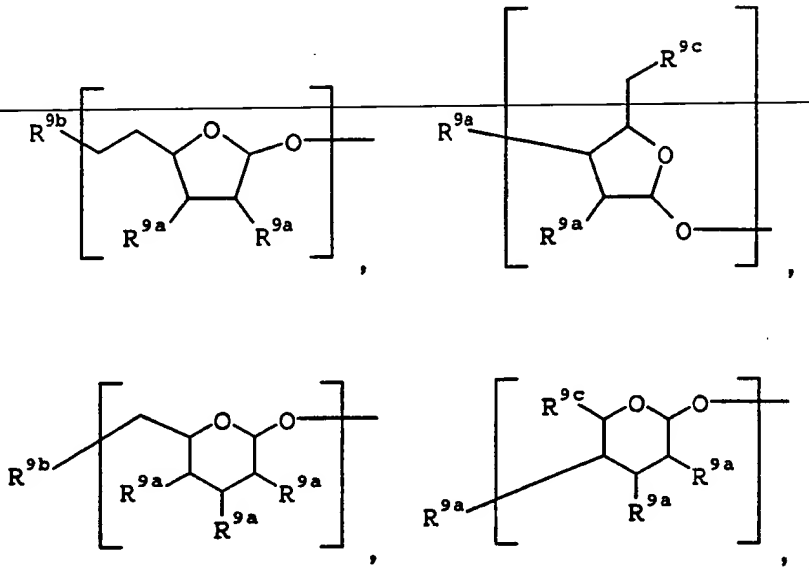
t is an integer from 2-7;

R^8 is a sugar moiety of the formula



where R^9 is independently -H, -OH, $-N_3$, -O-Pg, $-NH_2$,

-NH-Pg, or a second sugar moiety comprising one to three sugar units selected from the group consisting of



and mixtures thereof, wherein

R^{9a} is -H, -OH, $-N_3$, $-NH_2$, -O-Pg, or -NH-Pg,

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg,

R^{9c} is $-CH_3$, $-CH_2OH$, $-CH_2N_3$, $-CH_2OSO_3H$, $-CH_2NH$-Pg, $-CH_2O$-Pg, $-CO_2H$, or $-CO_2$-Pg,

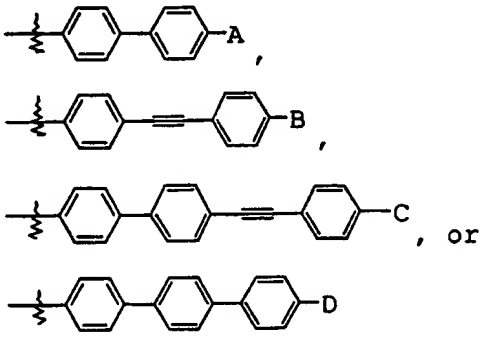
where R^a is as defined above,

and so long as no more than one R^9 is represented by said second sugar moiety;

Pg is a protecting group; and

pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

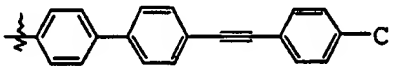
9. The Method of Claim 8 wherein R is

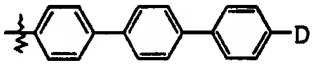


where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or
-O-$(CH_2)_m$-$[O$-$(CH_2)_n]_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E;
m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;
X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

10. The method of claim 8 wherein the recipient is a human.

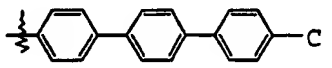
11. The method of Claim 9 wherein
R^1 is hydroxy at each occurrence;
R^4 is hydroxy;
R^5 is -OPO_2HR^a, where R^a is methyl or methoxy;
R^2, R^3, and R^7 are each methyl; and
R is a moiety of the formula


, or

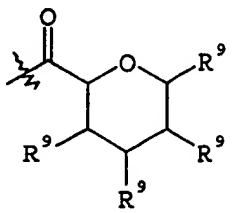

; or

a pharmaceutically acceptable salt or solvate thereof.

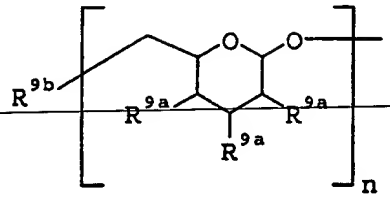
12. The method of Claim 9 wherein
R^5 is hydroxy;
R is a moiety of the formula


,

where C is hydrogen or C_3-C_7 alkoxy;
R^8 is a moiety of the formula


,

where R^9 is independently hydrogen, hydroxy, amino. or a moiety of the formula



; and

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg and n is 1, 2, or 3; or

a pharmaceutically acceptable salt or solvate thereof.

13. The method of Claim 12 wherein

C is n-pentoxy;

R^9 is independently hydroxy or amino; or a pharmaceutically acceptable salt or solvate thereof.

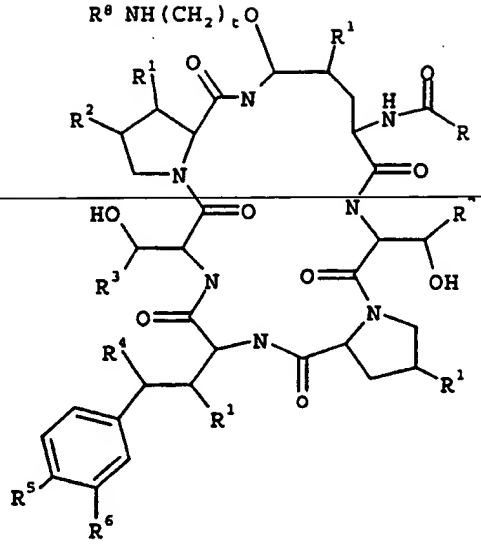
14. The method of claim 13 wherein

R^9 is hydroxy at each occurrence; and

t is 2; or a pharmaceutically acceptable salt of solvate thereof.

15. The method according to Claim 8 wherein the fungal activity arises from one or more of the fungi selected from the group consisting of *Candida albicans, Aspergillus fumigatis*, and *Candida parapsilosis*.

16. A method of inhibiting parasitic activity comprising administering to a recipient in need of such inhibition an effective amount of a compound represented by structure I:



wherein

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group;

R^1 is independently -H, -OH or -O-Pg;

R^2 is -H, $-CH_3$, $-NH_2$, or -NH-Pg;

R^3 is -H, $-CH_3$, $-CH_2CONH_2$, $-CH_2CONH$-Pg, $-CH_2CH_2NH_2$, or $-CH_2CH_2NH$-Pg;

R^4 is -H, -OH, or -O-Pg;

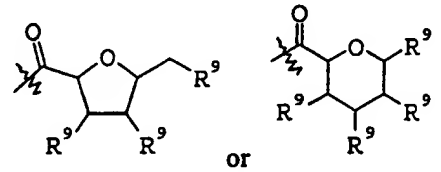
R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy;

R^6 is -H, -OH, or $-OSO_3H$;

R^7 is -H or $-CH_3$;

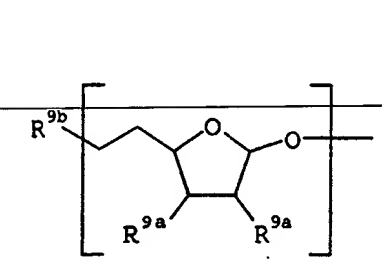
t is an integer from 2-7;

R^8 is a sugar moiety of the formula



where R^9 is independently -H, -OH, $-N_3$, -O-Pg, $-NH_2$,

-NH-Pg, or a second sugar moiety comprising one to three sugar units selected from the group consisting of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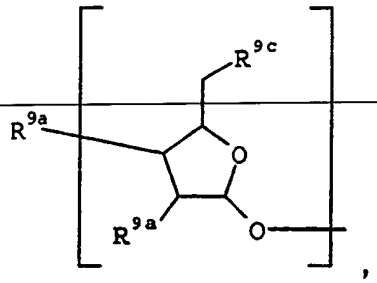
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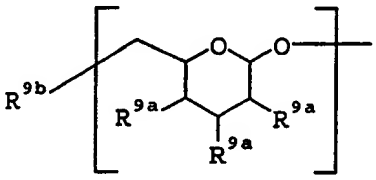
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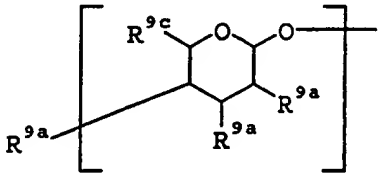

, and mixtures

thereof, wherein

R^{9a} is -H, -OH, $-N_3$, $-NH_2$, -O-Pg, or -NH-Pg,

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg,

R^{9c} is $-CH_3$, $-CH_2OH$, $-CH_2N_3$, $-CH_2OSO_3H$, $-CH_2NH$-Pg, $-CH_2O$-Pg, $-CO_2H$, or $-CO_2$-Pg,

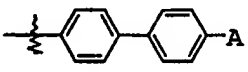
where R^a is as defined above,

and so long as no more than one R^9 is represented by said second sugar moiety;

Pg is a protecting group; and

pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

17. The Method of Claim 16 wherein R is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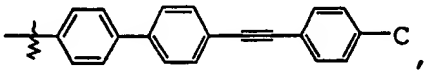
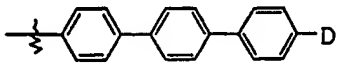

, or



where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}$ alkyl) or $-O-(CH_2)_q-X-E$;

m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4:

X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

18. The method of claim 16 wherein the recipient is a human.

19. The method of Claim 17 wherein

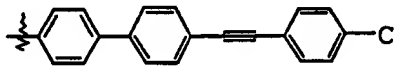
R^1 is hydroxy at each occurrence;

R^4 is hydroxy;

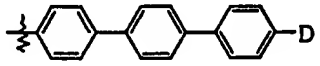
R^5 is $-OPO_2HR^a$, where R^a is methyl or methoxy;

R^2, R^3, and R^7 are each methyl; and

R is a moiety of the formula



, or



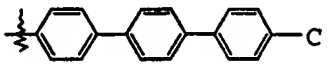
; or

a pharmaceutically acceptable salt or solvate thereof.

20. The method of Claim 17 wherein

R^5 is hydroxy;

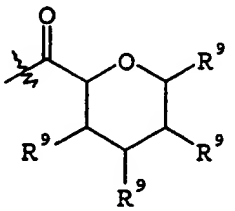
R is a moiety of the formula



,

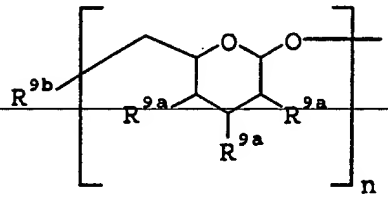
where C is hydrogen or C_3-C_7 alkoxy;

R^8 is a moiety of the formula



,

where R^9 is independently hydrogen, hydroxy, amino. or a moiety of the formula



; and

R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg and n is 1, 2, or 3; or

a pharmaceutically acceptable salt or solvate thereof.

21. The method of Claim 20 wherein

C is n-pentoxy;

R^9 is independently hydroxy or amino; or a pharmaceutically acceptable salt or solvate thereof.

22. The method of claim 21 wherein

R^9 is hydroxy at each occurrence; and

t is 2; or a pharmaceutically acceptable salt of solvate thereof.

23. The method of Claim 16 wherein the parasitic activity arises from *Pneumocystis carinii*.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 99/29927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/56 A61K38/12 A61P31/10 A61P33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 757 058 A (LILLY CO ELI) 5 February 1997 (1997-02-05) the whole document	1-23
P,Y	WO 99 43337 A (LILLY CO ELI ;JAMISON JAMES ANDREW (US); RODRIGUEZ MICHAEL JOHN (U) 2 September 1999 (1999-09-02) the whole document	1-23
A	WO 97 17365 A (MERCK & CO INC ;BALKOVEC JAMES M (US); BOUFFARD FRANCES A (US); DR) 15 May 1997 (1997-05-15) the whole document	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2000	16/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/29927

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 99/29927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0757058 A	05-02-1997	US 5629289 A	13-05-1997
		AU 6593896 A	26-02-1997
		JP 11510165 T	07-09-1999
		WO 9705163 A	13-02-1997
WO 9943337 A	02-09-1999	AU 2686099 A	15-09-1999
		EP 0943623 A	22-09-1999
WO 9717365 A	15-05-1997	AU 707664 B	15-07-1999
		AU 7554096 A	29-05-1997
		EP 0862579 A	09-09-1998
		HR 960521 A	30-04-1998
		JP 2000501076 T	02-02-2000